PSJ17 Exh 55

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Carol S. Marchione
Senior Director, Regulatory Affairs
Cephalon, Inc.
145 Brandywine Parkway
West Chester, PA 19380

RE: NDA # 20-747
Actiq® (oral transmucosal fentanyl citrate)
MACMIS # 12641

Dear Ms. Marchione:

Please refer to the meeting between representatives of your firm and DDMAC on August 30, 2004. The purpose of the meeting was to discuss Cephalon's concerns with the DDMAC review process for Actiq and to discuss DDMAC's concerns with Cephalon's promotional activities for Actiq.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact me by facsimile (301) 594-6771, or write to me at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #12641 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Brenda Marques
Senior Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
Office of Medical Policy
Center for Drug Evaluation and Research

Enclosure

NDA 20-747

INDUSTRY MEETING MINUTES

Meeting Date: August 30, 2004

Location: Parklawn Building, Conference Room M

NDA/ Name: NDA 20-747

Sponsor: Cephalon, Inc.

Drug: Actiq (oral transmucosal fentanyl citrate)

Type of Meeting: Requested by Cephalon and DDMAC in follow-up to July 14, 2004 meeting

Meeting Chair: Thomas Abrams, Division Director
Division of Drug Marketing, Advertising, and Communications
HFD-42

External Lead: Carol Marchione, Senior Director, Regulatory Affairs
Cephalon, Inc.

Cephalon Inc.	Title
Ed Berg	Associate General Counsel
Carol Marchione	Sr. Director, Regulatory Affairs
Greg Martin	Director, Sales Operations
Tracie Parker	Sr. Manager, Regulatory Affairs
Andy Pyfer	Actiq Product Director
Robert P. Roche, Jr	Senior Vice-President, Pharmaceutical Operations
DDMAC	**Title**
Thomas Abrams	Division Director, DDMAC
Carol Barstow	Special Assistant to Director, DDMAC
Kristin Davis	Regulatory Counsel, DDMAC
Spencer Salis	Group Leader, DDMAC
Brenda Marques	Senior Regulatory Review Officer, DDMAC
Jialynn Wang	Senior Regulatory Review Officer, DDMAC

Background:

Following a July 14, 2004 meeting between Cephalon, the Division of Anesthetics, Critical Care, and Addiction Drug Products (DACADP) and the Division of Drug Marketing, Advertising, and Communications (DDMAC), Cephalon requested a follow-up meeting with DDMAC to discuss its

concerns regarding the review process for its promotional pieces. DDMAC agreed to meet with Cephalon and also stated that it would like to discuss various concerns DDMAC had regarding the promotion of Actiq, including concerns regarding information about Cephalon's promotion that was provided by Cephalon during the July 14, 2004 joint division meeting and in Cephalon's briefing package for the July 14, 2004 meeting.

Meeting Objectives:

To discuss the respective concerns of DDMAC, regarding Cephalon's promotional materials and practices for Actiq, and of Cephalon, regarding the DDMAC review process for providing advisory comments on Actiq promotional pieces.

Discussion Points:

A. DDMAC's concerns regarding:
- off-label use of Actiq
- the targeting criteria and lack of screening for physicians called upon by Cephalon's sales force to promote Actiq
- training/detailing practices which inappropriately broaden the drug's labeled indication
- the eliciting of and response to off-label inquiries regarding Actiq
- minimizing the fatal risk of Actiq to children
- the promotional use of disease awareness materials that discuss conditions for which Actiq is not indicated to treat

B. Cephalon's concerns regarding and requested revisions of DDMAC's review process for providing advisory comments, including:
- changes in opinion
- timing of teleconferences following a request for clarification of DDMAC comments
- early review of templates whose purpose is to ensure safe opioid prescribing or communicate a public health concern
- annual meeting regarding the review of future promotional pieces

Discussion:

A. Concerns Regarding Promotion

1. DDMAC expressed significant concerns about the increasing off-label use of Actiq, particularly in light of the Risk Management Plan (RMP) that is in effect for Actiq, which mandates that, among other things, the company act to prevent against improper patient selection. DDMAC reminded Cephalon that off-label promotion is illegal and, especially with a drug with a risk profile like Actiq, raises significant public health concerns. As discussed further below, DDMAC expressed concerns that Cephalon's training and detailing practices appear to encourage the off-label use of Actiq rather than discourage it.

In response to these concerns, Cephalon stated that, in an effort to comply with the provisions of the RMP, it communicates both verbally and in writing with physicians who prescribe Actiq off-label, and in those communications it conveys Actiq's indication and risk information about Actiq.

2. DDMAC expressed concerns that, as indicated by Cephalon's briefing package for and presentation at the July 14, 2004 meeting, the company targets physicians for Actiq promotion purely based on the number of opioid prescriptions they write, and the company is making no effort to screen these targeted physicians to determine whether they treat cancer patients and thus would be appropriate to be detailed on Actiq given its limited indication – i.e., management of breakthrough cancer pain (BTCP) in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Actiq's briefing package (at p. 598) and comments made by Cephalon at the July 14th meeting indicate that Cephalon's sales representatives are calling on physicians who are not treating BTCP and who are not prescribing Actiq already. This is especially concerning as many of the targeted specialty areas, such as physical medicine specialists, do not routinely treat cancer patients. There does not appear to be any reason for these sales calls other than to promote Actiq outside its labeled indication and the fact that off-label prescriptions have increased in such specialty areas seems to add validity to this conclusion. This is particularly concerning given the risk profile of Actiq. In addition, DDMAC expressed concerns regarding Cephalon's stated reason at the July 14th meeting for sending sales representatives to call upon physicians who were clearly using Actiq off-label, namely, to provide risk information to help ensure safe use of the drug. While DDMAC acknowledged how important it is that these physicians receive information from Cephalon regarding the serious risks associated with using this drug, as per the RMP, DDMAC questioned whether having the promotional arm of the company – the sales force – repeatedly call on these physicians was the most effective way of communicating risk information and whether it would not also potentially encourage rather than discourage the off-label uses, which would violate the principles of the RMP.

In response to these concerns, Cephalon indicated that the company takes the law applying to promotion very seriously, and trains its sales force to comply with the law. Cephalon confirmed that it does target physicians in various specialties by their opioid prescribing practices regardless of whether they treat cancer patients or cancer pain. Specifically, physicians who write at least 24 opioid prescriptions in 6 months are targeted for a sales call by a Cephalon sales representative. The company believes it is a good idea to call on physicians who do not treat BTCP based on its belief that such calls can encourage these physicians to treat this condition should they see it in their practice. The company also stated its belief that a physician did not need to "routinely" see cancer patients to be an appropriate target for an Actiq sales call. Cephalon also confirmed that its sales representatives will make repeated sales calls to targeted physicians who are not using Actiq for the treatment of BTCP. Cephalon also indicated its belief that, in addition to communications from its Medical department, sending its sales representatives to call on physicians who were using Actiq off-label was an effective way of communicating important risk information to these physicians and did not encourage off-label use, though they would consider DDMAC's comments on the issue. Cephalon also noted its belief that the RMP does not require the company to discourage off-label use of Actiq. While noting that it does not promote Actiq off-label, Cephalon stated its belief that pain in general is an undertreated medical need and that Actiq can be used safely and effectively for other uses than BTCP; the company will be pursuing a broadened indication for the drug.

3. DDMAC expressed concerns that Cephalon, as indicated in the briefing package for the July 14, 2004 meeting (see, e.g., p. 191) and in its presentation at the meeting, is instructing its sales force to open sales calls in a manner that fails to focus on Actiq's limited indication and instead focuses on the physician's treatment of breakthrough pain (BTP) in general, thus inappropriately broadening physicians' perceptions of the drug's use to the treatment of all forms of BTP, rather than BTCP in the indicated population. Specifically, the sales training materials offer "verbatims" designed to assess the physician's treatment of BTP, then the materials discuss the characteristics of BTP and the characteristics of the "Ideal Breakthrough Pain Medication," which would lead to a discussion of the specific benefits of Actiq.

Moreover, related to the points discussed above, DDMAC noted that the practice "verbatims" in the sales training materials did not ask any questions of the physician to determine whether he or she routinely saw cancer patients or treated BTCP. DDMAC noted that the sales training materials, in their totality, do train on providing the indication for the drug during the sales call, however, DDMAC further noted that simply presenting Actiq's indication during the sales call did not insulate other parts of the detail visit from being considered off-label promotion should the sales representative focus his or her detail for Actiq on treating BTP in general rather than in treating cancer patients with BTCP. DDMAC also stated that, though it acknowledges that companies may, for educational purposes, choose to train sales representatives on a broader therapeutic area than their products are indicated for, the Actiq sales training materials in their entirety seem to convey Cephalon's strong belief that Actiq is safe and effective and appropriate for treating a wide variety of pain conditions, thus potentially encouraging such promotion. This is especially concerning in light of the boxed warning and other risk information associated with the drug, which indicates that, among other things, the drug should not be used in opioid non-tolerant or naïve patients because of the risk of life-threatening hypoventilation.

In response, Cephalon stated that it trains its sales representatives to always provide the labeled indication for Actiq during its sales calls and promote only Actiq's labeled indication, though it educates them on the therapeutic area of pain in general. Cephalon stated that a sales representative may begin a sales call with a broad discussion of BTP and transition to a discussion of Actiq as a medication to treat BTCP.

4. DDMAC expressed concerns that, as indicated by Cephalon's briefing package for and presentation at the July 14, 2004 meeting, the company is training its sales force to detail doctors in a manner that elicits off-label inquiries and to respond inappropriately to these inquiries from doctors regarding off-label use (see, e.g., pp. 237-9, 241). DDMAC indicated that Cephalon's apparent practice of training its representatives to broadly discuss BTP in sales calls appears to invite or solicit requests from physicians regarding off-label uses of the product. DDMAC also stated that it would like to see the materials the company's sales representatives are trained to refer physicians to in response to questions about off-label uses of Actiq (e.g., materials referenced at pp. 237-9, 241 of briefing package related to uses such as migraines and back injury). DDMAC stated that, although the responses to off-label questions provided in the sales training materials include a statement of the indication, no risk information is provided regarding the off-label use and, moreover, the rest of the response appears to suggest a strong medical basis for and encourage the off-label use, which is concerning, especially given the RMP.

Cephalon indicated that its representatives are trained to convey Actiq's labeled indication, and that it believes that it is difficult to determine in some cases where the line between solicited and unsolicited requests is. Cephalon acknowledged that a discussion of BTP in general which transitioned into a discussion of the benefits of Actiq could cross the line into off-label promotion. Cephalon agreed to submit the requested materials to DDMAC.

5. DDMAC expressed concerns that, as indicated by Cephalon's briefing package for the July 14, 2004 meeting, the company is training its sales force to promote Actiq in a manner that minimizes the potentially fatal risk that this product poses to children (see p. 228), in disregard of the RMP and of the safety concerns for this vulnerable population that were an important part of developing the RMP. Specifically, the "standard response" provided in the sales training materials for sales representatives to use when faced with a doctor stating that he or she would not prescribe Actiq because it is too dangerous for children includes statements such as "ACTIQ is no more dangerous than any other med," "ACTIQ is not perceived as 'candy' by most kids," and "child likely to doze off and stop sucking unit, or if chewed, 2/3 lost to first-pass effect."

Cephalon agreed with DDMAC's concerns regarding this material and stated that these were inappropriate responses to such a question. Cephalon noted that it was not using this response in sales training and was currently working to revise its sales training materials accordingly.

6. DDMAC expressed questions and concerns regarding how Cephalon's sales force is using "disease awareness materials" that discuss broad conditions, such as BTP, that would go beyond Actiq's indicated use. DDMAC noted that if these materials were used during Actiq sales calls to lead into a discussion of Actiq, it could constitute off-label promotion. When viewed in totality with the concerning promotional practices discussed above, these materials appear to be designed to encourage discussions on conditions broader than Actiq's limited indication during sales calls, and could easily facilitate promotion of off-label uses of Actiq. DDMAC also noted that, per Cephalon's letter in the briefing package sent in preparation for the July 14, 2004 meeting, the company does not provide specific instructions to its sales representatives regarding simultaneous dissemination of branded and unbranded materials.

Cephalon indicated that an unbranded BTP brochure may be presented in a sales call where Actiq is discussed but that these brochures are not designed to be used in promotion of Actiq or to encourage off-label uses. They are intended to encourage awareness and treatment of BTP generally.

In response, DDMAC reminded Cephalon that the promotion of the drug by sales representatives must comply with the requirements that apply to all promotion, which include limiting promotion to Actiq's labeled indication and not suggesting off-label uses; "disease awareness materials" may not be used as an indirect way to promote or solicit questions on off-label uses.

B. Review Process

1. Cephalon indicated that it was concerned about changes of opinion in advisory comments DDMAC had provided for Actiq's promotional materials, particularly as it had assumed that once it applied DDMAC's comments to pieces, its pieces were in compliance with the law.

In response, DDMAC noted that it has the regulatory authority to issue changes of opinion when evaluation of publicly disseminated promotional materials that had been previously submitted for comment indicates that the materials are not in compliance with the law and regulations. DDMAC appreciates that changes of opinion significantly impact a sponsor, and therefore works to minimize the frequency of such changes and provide sponsors a reasonable timeframe, such as 90 days, to implement such changes. However, changes of opinion are necessary to ensure that promotional materials are in compliance with the law.

DDMAC also expressed its concern regarding Cephalon's practice of repeatedly submitting advisory materials that contain claims, omissions or presentations that DDMAC has objected to in past comment letters, as this practice wastes valuable time and resources. DDMAC reinforced that its past comments should be applied to all of Cephalon's promotional materials that contain the same or similar claims or presentations in order to have an efficient review process. DDMAC may send advisory materials back for revision if they perpetuate past objectionable claims or presentations.

2. Cephalon requested that, should it require clarification of DDMAC's advisory comments on draft promotional materials, DDMAC agree to make itself available so that a teleconference could occur within 10 days of the sponsor's request for clarification.

In response, DDMAC declined this request, pointing out that it had always had teleconferences with Cephalon in a timely fashion in the past when clarification was requested and needed, and that a formal change in the timeframe for such a meeting would be inconsistent with DDMAC's practice with regard to other sponsors, including those that have drugs approved under Subpart H. The sponsor is advised to incorporate DDMAC's review timeframe into its plans for submission of future promotional pieces.

3. Cephalon requested that DDMAC agree to pre-review and provide advisory comments on templates designed by the company to be sent out when necessary to ensure safe opioid prescribing or communicate a public health concern, so that, should a need arise for such materials, they could be sent out in an expedited fashion.

DDMAC stated that it is willing to provide comments in an expedited fashion for a proposed template or other communication that focuses solely on safety issues for Actiq (rather than communications which include a promotional message with safety information) in the interests of public health. However, DDMAC noted that its ability to review a template may depend on the nature of the information that is left blank to be filled in; if text, rather than just names, addresses and dates, is to be inserted, DDMAC would need to see the text options. Cephalon should also note that a later change in content of such materials may change the interpretation of the piece and therefore would require additional review by DDMAC. To expedite any additional review process, Cephalon should note changes from the original template in future submissions.

4. Cephalon requested that DDMAC agree to meet with the company annually in order to help DDMAC and Cephalon calculate the review time necessary for future planned promotional campaigns/pieces.

DDMAC agreed that it may be fruitful to hold an annual meeting. DDMAC noted, however, that comments on specific promotional claims and presentations could only be made in context and therefore promotional pieces should be submitted for advisory comments in accordance with normal procedures.

Summary

DDMAC summarized that it is concerned about the promotion of Actiq and is monitoring this promotion very closely. DDMAC also noted that FDA is prepared to take whatever action is necessary to address any violations and ensure that Cephalon complies with the law and that the public health is protected. Cephalon should also be aware that DDMAC has received complaints about its promotion, and that it is under scrutiny by others who are concerned about the potential for harm to the public health from inappropriate use of Actiq. Cephalon is strongly advised to take whatever steps are necessary to ensure that it is in compliance with the law.

DDMAC noted its appreciation for Cephalon's willingness to hear DDMAC's concerns and engage in discussion on these important issues regarding promotion of Actiq. Cephalon noted its appreciation for DDMAC's willingness to discuss Cephalon's concerns regarding the review process for advisory comments on draft promotional pieces and its request for future annual meetings with DDMAC on this issue.

Action Items

1. Cephalon will send DDMAC copies of the aforementioned materials that the company's sales representatives are trained to refer physicians to in response to questions about off-label uses of Actiq (e.g., materials referenced at pp. 237-9, 241 of briefing package).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Brenda Marques
9/20/04 05:05:04 PM

Note Regarding Actiq Algorithm

Please note that since we revised the prescribing information for our Gabitril product due to new warning information, we are currently in the process of revising this training piece to remove mention of other Cephalon products.